2017.6.18

China QA Forum

申办者自查的策略

中国质量保证论坛（CQAF）自查讨论总结

在今年CQAF上海年会期间，会员就申办者如何遵照2015年7月22日发布的“国家食品药品监督管理总局关于开展药物临床试验数据自查核查工作的公告（2015年第117号）”开展自查进行了讨论，讨论内容总结如下。

注：本文中的自查是指药品注册申请人，对待审药品注册申请的药物临床试验开展自查，不包括临床试验机构对本机构临床试验的自查。

English

1. 什么时候进行自查?

自2015年7月22日，国家食品药品监督管理总局（以下简称“总局”）要求药品注册申请人对已申报的待审注册申请开展自查，根据自查情况向审核查验中心（CFDI）提交自查报告。对于自查中发现数据存在不真实、不完整等问题的，申请人可以向总局提出撤回注册申请。自查的目的在于收集并确认自查报告所需提交信息的准确性，评估试验数据质量，判定是否有信心接受CFDI的临床试验数据现场核查。

对于正在进行中的研究或新的研究，我们建议将总局发布的《药物临床试验数据现场核查要点》中的相关要求融入常规监查活动中，确保临床试验数据质量在任何时候都符合核查标准，经得起检查/核查（inspection ready at all times）。具体建议如下：

- 关注源文件/HIS/LIS中受试者的医疗信息，确认研究中心记录受试者的身份证号，必要时试验用药在运送过程中有温度监控并有记录，生物样本的处理流程及记录；
- 发现的问题及时沟通并记录，在研究中心关闭之前即完成自查报告（这亦是目前研究中心对申办方的要求）；或中期分析锁库前（用中期分析结果递交NDA的试验）。研究中心关闭之后无需额外访视。

对于已完成的研究，可以基于研究实施过程中的监查和稽查情况，对数据质量进行初步判断后，结合资源以及完成自查的时限等实际情况，进一步决定自查是否需要去研究中心（现场）还是远程（非现场）。关键是能够在规定的时限递交报告，且确保一旦发现存在影响受试者安全和数据可靠性的重大问题，仍有时间来决定是否撤回申请。

如果研究者/研究机构认为有必要请第三方稽查，需要事先得到申办者的同意。因为试验项目稽查是申办者的职责，第三方稽查是代表申办者进行的稽查。

内容

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2. 如何发现和评估问题？

如上所述，对于正在进行的/新的研究，建议将自查内容融入常规监查活动。

对于已经完成的研究，开展自查前应回答的问题包括：是否有必要去现场进行自查？选择多少中心以及如何选择？是否需要进行re-SDV？如需要，是全部数据都进行re-SDV，还是对受试者进行抽样，或是选择部分数据抽样，抽样的百分比？

建议首先对试验层面的申办者研究文件进行审阅（in-house file review），审阅内容包括但不限于：

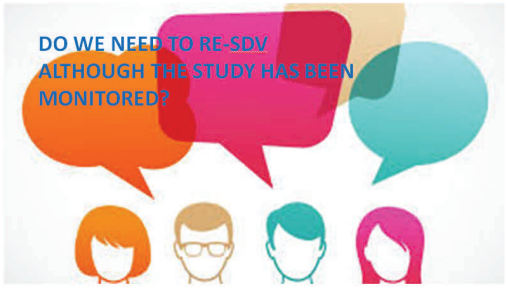
- 临床试验总结报告（CSR）：报告中述及的严重不良事件，问题，方案偏离，分中心报告等，并与其他相关信息进行比对，如与数据库中的SAE报告核对（reconciliation）以识别是否存在漏报；可以从中获得线索，即哪些情况需要进一步调查和跟踪。
- 必要文件（Trial Master File, TMF）：管理性文件如伦理批件， 临床试验批件等；
- 监查报告和稽查报告：了解主要研究者和研究中心的试验实施情况，作为依据选择试验中心进行自查，以及re-SDV/原始文件审阅（source document review, SDR)的百分比，同时可了解整体监查实施情况。

基于上述文件审阅中得到的信息及发现的潜在问题，决定是否需要开展研究中心的现场自查。具体的自查计划很大程度上取决于公司对风险的容忍度，以及对于存在问题的认知度。自查活动应确保收集的信息，能够帮助判断问题对受试者权益以及数据真实性的影响，并足以来判断是否要撤回注册申请。

对于正在进行的/新的研究，建议将自查内容融入常规监查活动。

3. 是否需要re-SDV?

Re-SDV (Source Data Verification) 的目的是发现原始数据与被输入CRF并最终反映在CSR中的数据之间的不一致。在决定re-SDV前需要考虑的风险因素包括：



- 主要研究者/研究机构、CRO/中心实验室的经验和表现；
- 试验是否由CRO负责监查，监查员更替的次数，监查质量；
- 在研期间公司质量管理体系（QMS）是否完善；
- 公司的风险容忍度

如果对上述情况没有一点线索，可考虑先进行小样本re-SDV。

一般而言，不建议试验结束后re-SDV，因为SDV是常规监查的一部分，应在试验实施过程中保证数据收集和报告的准确性，而不是在数据已经锁库、分析、报告给CFDA之后。除非是对数据记录和转抄的质量有很大担心，否则公司有可能陷入两难的境地：是否向CFDA 报告在re-SDV中发现的小问题。

决定进行部分或全部数据re-SDV前，建议公司内部所有相关部门参与讨论，必要时获得上级管理层的批准。因为：

- 该决定将对公司的资源和预算产生重大影响；
- 发现严重数据不一致时所产生的连锁反应，如漏报不良事件、合并用药等，将导致重新打开数据库（unlock the database），重新进行统计分析和撰写CSR，将问题报告给CFDA等等，这将大大延后注册申请的提交和批准，并可能影响监管部门对公司临床试验质量的信心。

4. 如何汇总和解决自查中发现的问题？

汇总问题：

- 问题的汇总方式应该服务于目的 （fit for purpose）；
- 建议集中对问题进行记录和跟踪，跟踪记录包括的基本信息有：问题描述，问题的重大程度，需要采取的行动及责任人（当地或总部）；是否需要上报 （上级管理层），结论 （结果）/备注（如报告CFDA， 剔除问题数据，重新统计和撰写CSR等）；
- 对于问题的分级要谨慎以避免混淆。必要的话需要提供分级的定义。

总的来说，明确自查的目的。如果申办者的 QMS足够完善，那么核查前的访视/稽查都不是必要的。

解决问题：

- 抓紧时间解决问题至关重要 - 因为现场核查近在眼前，况且研究已经结束，可做的事情非常有限；
- 要求研究中心重新熟悉研究及试验中出现的所有问题为核查做好准备。申办者的人员可以要求研究者回忆试验当时情况，但是不可以为研究者提供答案，因为这是研究者的职责；
- 关注重点问题，尽量了解问题的全部信息，公司所有的相关部门都要参与讨论，评估对研究结论的影响，并做出是否撤回的决定；
- 恰当地解决问题：对于那些没有明确答案的问题，尽可能的去收集所有与问题有关的信息。例如，室温保存的药物在运输过程中没有温度记录，准备好稳定性报告，了解运输持续时间，研究期间的天气因素等。希望使检查员信服，即虽然没有运输温度记录，但研究用药在整个试验期间是保存在适合的温度条件下的；
- 发现重大问题时，建议及时与CDE沟通听取意见，例如剔除数据，重新撰写CSR等；
- 不要为了改正小错误而犯更大的错误，例如为遗漏的信息编造数据；
- 可以根据公司内部相关政策和流程制定整改和预防措施（corrective actions and preventive actions），但由于时间紧迫，建议把这部分工作放到核查结束后的分享学习中；
- 问题报告给CFDA：在何时/什么情况下需要向CFDA报告？如果CFDA有相关规定，就按照CFDA的要求报告；如果没有明确的法规，则按照公司策略或相关部门集体讨论后的决定。或许没有必要向CFDA汇报较小的问题，但对研究结论有潜在影响的问题及时报告CFDA是非常重要的；

总的来说，明确自查的目的。如果申办者的 QMS足够完善，那么核查前的访视/稽查都不是必要的。

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Strategy on the management of Self -inspection

Summary of CQAF workshop

Chinese

During the recent China QA Forum Face-to-Face meeting on 25 May, a workshop was organized to discuss how to manage self-inspection in China in reflection of CFDA self-inspection requirements issued on 22 Jul 2015. Below is the summary of the discussion:

Note: Self-inspection in this article refers to sponsor's activities to identify and report issues occurred in the study to CFDA via submitting the self-inspection report for studies that have been submitted to CFDA but pending for the agency's approval.

1. When to conduct self-inspection?

The purpose of self-inspection is to meet CFDA's requirement on submitting self-inspection report (to disclose issues during the study) as part of the NDA approval and assure data integrity for the upcoming NDA pre-approval inspection. So we suggest to embed this requirement in routine monitoring /co-monitoring visits for ongoing and new trials, to achieve inspection readiness at all times:

- During routine site monitoring: pay sufficient attention to CFDA requirements on source document/ verify subject information in HIS and LIS, subject ID; temperature records during IP shipment as necessary, and sample handling procedures
- Capture issues on an on-going basis and summarize them before site closure (which is mandatory by investigator site)/interim database lock, so self-inspection report is ready for submission at anytime, and no additional visit by the sponsor/CRO will be required after site closure.
- It is important to work /align with investigators on issues/solutions. If 3rd party audit is deemed necessary, it should be performed on behalf of and agreed by sponsor as this is sponsor's responsibility.
- For completed studies, the level of activities needed will depend on how confident the sponsor/ CRA is with the data/investigator sites' performance; resource at sponsor, self-inspection can be on site visit, or remote… Key is to meet the timeline for reporting, and decide whether or not to withdraw the application because of significant issues relating to patient safety and/or data integrity.

Content

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2. How to identify and assess issues?

As mentioned above, for on-going /new studies, self-inspection should be embedded in routine monitoring.

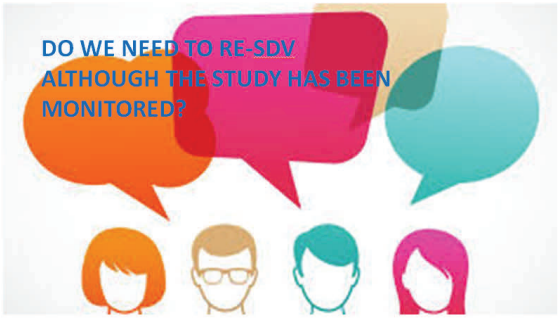
For completed studies, there are questions around: how many/which site or vendor should be selected for self-inspection, if re-SDV should be performed, % of re-SDV to be performed. This largely depends on company risk tolerance, current knowledge of existing gaps and evaluation of issues identified during in-house review of study documents. The level of activities should be tailored to ensure collection of adequate information to enable the assessment on whether or not to withdraw the NDA application due to significant concerns around patient safety and/or data integrity.

It is suggested to conduct in-house study/site level document review to assess the risks to determine the necessity to conduct the self-inspection on-site. In-house study/site level document review includes CSR, TMF, PI and vendor performance etc. where data were generated. For example:

- CSR review should include SAE, Issue log, PD logs, Center reports, to get clues on the need for further check, e.g. reconciliation of SAE listing will help to identify unreported SAEs (if any)
- TMF: management documentation: IRB, CTA approvals etc.
- Monitoring visit reports: to assess PI's performance , to decide selection of site for self-inspection, and also % of SDV/SDR during the site visit

For on-going /new studies, self-inspection should be embedded in routine monitoring.

3. Do we need to re-SDV?



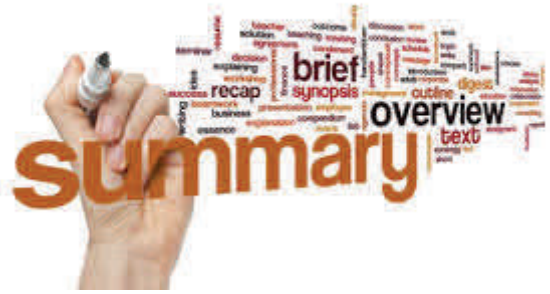
The purpose of re-SDV is to find out inconsistency between source data and data entered into CRF which were subsequently reflected in CSR. Risk factors to consider prior to the decision of re-SDV are: Investigators', monitors' and lab's experience and performance, availability of resources , # of monitor's handovers, robustness of company QMS during study, company risk tolerance level and result of in-house study file review. If you do not have the above information, you may select a small sample for re-SDV to make the evaluation.

- In general, it is not suggested to re-SDV. Because this is already covered during routine monitoring; all data were processed, analyzed and reported to CFDA. Unless there is significant concern on the quality of data transcription, otherwise company may run into the dilemma of whether or not to report minor discrepancies identified from re-SDV to CFDA
- There are situations that sponsor/CRO has to conduct re-SDV for some or all of the trial data. In this case, all stakeholders should be involved in the discussion and sometimes approval from senior management should be obtained because of:
    - ◊ The high consequence on resource and budget;
    - ◊ And if significant transcription errors (e.g. missing AE, Con Med) are identified, this may require the sponsor/CRO to unlock data base, re-do stats and CSR, reporting this to CFDA, delay in NDA submission and approval, as well as the potential impact on regulators' confidence on the quality of clinical studies sponsored by company

4. How to summarize and address the issues identified prior to inspection?

Summarize issues:

- Issues should be summarized in a way fit for purpose.
- Suggest to centrally track all issues, minimum information in the tracker includes: issue description; significance of the issue; action to take; action owners (local or global study team); escalation to senior management; outcome/comments (report to CFDA, remove data, re-do stats or CSR etc.).
- Be careful with the issue classification to avoid confusion. Provide definition of the classification if classification is deemed necessary.



In general, always remember the purpose of the self-inspection. Pre-inspection visit/audit may not necessary if sponsor employs robust QMS.

Address issues:

- Time is crucial in addressing issues as site inspection is coming soon. Also, there are not many things we can do as study has already completed.
- Suggest not develop CAPA due to time limitation, include it in lessons learned sharing session and implement CAPA if applicable post inspection
- Focus on significant issues, understand the full picture of the issues, involve relevant stakeholders to discuss the impact on study conclusion and decide if withdrawal or not
- Report issues to CFDA: when/in what situation you need to report to CFDA? Follow CFDA guidance if any on issue reporting. If no clear guidance, follow company strategy or decision from stakeholders' discussion. It may not be necessary to report minor issues to CFDA, but it is important to report issues that could potentially impact on study conclusion
- It is advisable to communicate with CDE of CFDA on significant issues that have identified, to get advice on possible actions… e.g. remove data, re-do CSR etc.
- Address the issues appropriately. For issues that you don't have a direct answer, try to find out all relevant information around the issue. For example, if there was no temperature recording during shipment for room temperature drug, you can find drug stability report, shipment duration, weather condition during study etc. Hopefully these can convince inspectors that the IP were still in condition fit for purpose even though there was no temperature records during shipment.
- Prepare the site staff for the inspection, re-familiarize with the study and all the issues during study. It should be made clear that sponsor staff must not provide answers to PI/site
- Don't make bigger mistake because of correcting a small mistake, i.e. make up data for missing information

In general, always remember the purpose of the self-inspection. Pre-inspection visit/audit may not be necessary if sponsor employ robust QMS.

CQAF aims to Promoting GxP Quality Standards in the Healthcare Industry

CQAF致力于在医药行业推广GxP领域的质量标准。

如果您有质量相关的问题，欢迎您通过www.cqaf.org或China QA Forum 微信公众号提出探讨，核心小组将每月汇总问题和答复并公布于www.cqaf.org或China QA Forum 微信公众号。

CQAF welcome you to pose your question via www.cqaf.org or China QA Forum official account, if you have any quality relevant question. CQAF Core team will summarize questions and answers monthly and publish them through www.cqaf.org or China QA Forum official account.

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